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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,769	HEYWOOD ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-7,21-38,41,43 and 45-47* is/are pending in the application.

4a) Of the above claim(s) *21-23 and 30-38* is/are withdrawn from consideration.

5)☒ Claim(s) *5-7* is/are allowed.

6)☒ Claim(s) *24-29,41,43 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 February 2009 has been entered.

2. Claims 1-4, 8-20, 39-40, 42 and 44 are cancelled.

Claims 24-26, 41 and 43 have been amended.

Claims 45-47 have been added.

3. Claims 21-23 and 30-38 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 5-7, 24-29, 41, 43 and 45-47 are under consideration.

5. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

6. The objection to claim 41 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in vie of the amendments to the claim.

7. The rejection of claim 18 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "in which one of said effector molecules is attached to each cysteine in the hinge" is withdrawn in view of the cancellation of the claim.

8. The rejection of claims 14-15 and 17-20 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "derivative thereof" is withdrawn in view of the cancellation of the claims.

9. The rejection of claims 24-29 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicants' arguments, i.e., Example 1 of the specification.

10. The rejection of claim 4 under 35 U.S.C. 102(b) as being anticipated by Carter P. J. (WO 93/06217, 4/1/1993) as evidenced by Bodmer et al (WO 89/01974) is withdrawn in view of the cancellation of the claim.

11. The rejection of claims 14-15, 17-19, 41 and 43 under 35 U.S.C. 102(b) as being anticipated by Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) is withdrawn in view of the cancellation of claims 14-15 and 17-19 and the amendments to claims 41 and 43.

12. The rejection of claim 4 under 35 U.S.C. 103(a) as being unpatentable over Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) in view of Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 42 filed 10/20/06) is withdrawn in view of the cancellation of the claim.

13. The rejection of claims 4, 14-15, 17-19, 41 and 43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) is withdrawn in view of the cancellation of claims 4, 14-15 and 17-19 and the amendments to claims 41 and 43.

Rejections Maintained and New Grounds of Objections/Rejections

14. The amendment filed 2/26/2009 is acknowledged, however, newly added claims 45-47 do not fully comply with 37 CFR1.121.

37 CFR1.121(c)(3) states:

> Any claim added by amendment must be indicated with the status of "new" and presented in clean version, *i.e.*, without any underlining.

37 CFR1.121(c)(2) states

> Since the text of any added subject matter must be shown by underlining the added text.

Thus, it is unclear what the underlining in newly added claims 45-47 represents since claims 45-47 are newly added. Applicants' cooperation is requested to ensure that future amendments comply with 37 CFR1.121 in the interest of compact prosecution.

15. The rejection of claims 24-29, 41, 43 and now applied to newly added claim 47 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "derivative thereof" in claims 24 and 41 is maintained.

The response filed 2/26/09 states that the term "derivative" is defined in the specification at pg. 8, lines 4-9 and which is sufficient to apprise one of skill in the art of the metes and bounds of the claims. This has been fully considered but is not found persuasive. The specification as pointed to by applicant defines the term "derivative" as follows:

> "Derivatives" as used herein is intended to include reactive derivatives, for example thiol-selective reactive groups such as an α-halocaraboxylic acid or ester, e.g. iodoacetamide, an imide, e.g. maleirnide, a vinyl sulphone or disulphide malemides and the like. The reactive group may be linked directly or through a linker segment to the polymer. It will be appreciated that the residue of such a group will in some instances form part of the product as the linking group between the antibody fragment and the polymer.

Thus, the definition provided in the specification would not apprise one skilled in the art of the metes and bounds of the claims since the term includes "reactive derivatives" and list some examples, however, the phrase "for example" renders the definition indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Additionally, the list of the examples includes "and the like", making it unclear what additional embodiments may be contemplated. Thus, one skilled in the art would not be reasonable apprised of the metes and bounds of the claims and the rejection is maintained.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

> such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. The rejection of claims 24-29 and now applied to claims 41 and 43 as presently amended and newly added claims 45-47 under 35 U.S.C. 103(a) as being unpatentable over Singh et al (Analytical Biochemistry, 304(2):147-156, May 15, 2002, cited on PTO-892 mailed 2/26/2008) in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) and Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 42 filed 10/20/06) is maintained and made again..

Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and selenol-catalyzed reduction of disulfide bonds in Fab fragments has previously been reported (see entire document, particularly

abstract, pp, 148, 154-155 and Fig. 1). Singh et al do not specifically teach an antibody comprising a Fab or Fab' fragment wherein the heavy chain in the fragment is not covalently bonded to the light chain and an effector molecule or polyethylene glycol (PEG) is attached to each of the interchain cysteines of CL and CH1, and wherein at least one further effector molecule is attached to a cysteine in the light chain constant region and/or to a cysteine in the heavy chain constant region, and wherein the fragment is a Fab' fragment that contains a modified hinge selected from SEQ ID Nos:1-14. These deficiencies are made for in the teachings of Hesi et al and Humphreys et al.

Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more polyethylene glycol (PEG) molecules via a cysteine residue or residues engineered into the hinge region wherein each PEG molecule may be 20,000 Da or 30,000 Da as well as pharmaceutical compositions comprising the anti-IL-8 antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer (see entire document, particularly pp. 21-38 and 104-105).

Humphreys teach Fab' hinge region peptides that efficiently generates dimers (e.g., di-Fab'), which are highly resistant to chemical reduction *in vivo* and the hinge peptides are well tolerated in *E.coli* and are non-immunogenic and the hinge region peptides of Humphreys are identical to the hinge regions of SEQ ID Nos:1-3 (see entire document, particularly pp. 2 and Table II). Humphreys also teaches that Fab' dimers comprising the modified hinge peptides can be reduced to expose reactive thiols to which one, two, three or more effector molecules, including PEG may be attached (e.g., see pg. 9, lines 2-5 and 34).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al, as well as pharmaceutical compositions comprising the PEGylated anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments and a pharmaceutically acceptable carrier or excipient for therapeutic benefit of inflammatory disorders.

One of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have produced anti-IL-8 Fab, Fab',

Fab-SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al, as well as pharmaceutical compositions comprising the PEGylated anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments and a pharmaceutically acceptable carrier or excipient for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys because Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules via a cysteine residue or residues engineered into the hinge region wherein each PEG molecule may be 20,000 Da or 30,000 Da, as well as pharmaceutical compositions comprising the anti-IL-8 antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer and Humphreys teach engineered Fab' hinge region peptides (i.e., SEQ ID Nos:1-3) that efficiently generates dimers (e.g., di-Fab), and the modified hinge peptides can be reduced to expose reactive thiols to which one, two, three or more effector molecules, including PEG may be attached. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising the cysteine containing hinge peptides of SEQ ID Nos:1-3 as taught by Humphreys and reduced using the selenol-catalyzed reduction of interchain disulfides to expose reactive thiols to which PEG molecules are attached since selenol-catalyzed reduction of interchain disulfides provides a rapid method in which the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and the method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial

result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Singh et al provides evidence that reduction of interchain disulfide bonds of an antibody does not result in a significant decrease in affinity or stability and selenol-catalyzed reduction of disulfide bonds in Fab fragments has been performed previously (Singh et al, pg. 148 1st col.). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al, as well as pharmaceutical compositions comprising the PEGylated anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments and a pharmaceutically acceptable carrier or excipient for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

The response filed 2/26/09 reiterates that at the time of the priority of the present application, one skilled in the art would not have attempted to attached PEG (or a derivative) to the interchain cysteines of a Fab or Fab' fragment because of the risk that the PEG would draw water away from the antibody fragment, creating destabilizing effect on the fragment that would force the heavy and light chains apart. Applicant states that the inventors discovered that, surprisingly, and contrary to prior perceptions in the art, an antibody fragment can be provided with PEG effector molecules attached to interchain cysteines, and the heavy and light chains remain associated with each other, such that the PEGylated antibody Fab' fragment has equivalent antigen binding and *in vivo* activity compared to PEGylated Fab' fragments in which the interchain disulphide bond is present. Applicants' arguments have been fully considered but are not found persuasive. Again, Applicants' arguments questioning the operability of the prior art, i.e., that PEGylation of the interchain cysteines would destabilize the antibody fragment and force the heavy and light chains apart, and applicants' allegations of the surprising and

unexpected discovery that an antibody fragment can be provided with PEG effector molecules attached to interchain cysteines, and the heavy and light chains remain associated with each other, such that the PEGylated antibody Fab' fragment has equivalent antigen binding and *in vivo* activity compared to PEGylated Fab' fragments in which the interchain disulphide bond is present are acknowledged, however, applicant is again reminded that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). See MPEP 716.01(c).

Applicant also again argues that Singh et al only describes the attachment of small molecules such as biotin to **a whole antibody**, not larger molecules such as PEG and Hesi teaches fragments in which one of the interchain cysteines has been substituted with serine, and no more than one polymer is attached to the fragment, the attachment being at the remaining interchain cysteine. Applicant states that Humphreys is concerned with the production of dimeric F(ab')2 fragments containing a specific hinge sequence having four cysteines and wherein **both** interchain cysteines have been replaced with serines and Humphreys makes no mention of fragments in which both the interchain cysteines were retained and have effector molecules attached and thus, combining Singh , Hesi and Humphreys would not result in the structure of claim 24, i.e., a fragment having PEG attached to **both** its interchain cysteines and there is no teaching or suggestion in the combined art to create such a structure. Applicants' arguments have been fully considered but are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re*

Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, in response to applicants' arguments that Singh et al is limited to the attachment of small effector molecules to whole antibodies, not fragments and Hesi only teaches the attachment of one polymer wherein attachment is at the interchain cysteine that is not substituted and that Humphreys discloses the replacement of both interchain cysteines with serine, applicant is reminded that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). See also *In re Sneed*, 710 F.2d 1544, 1550, 218 USPQ 385, 389 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review."); and *In re Nievelt*, 482 F.2d 965, 179 USPQ 224, 226 (CCPA 1973) ("Combining the teachings of references does not involve an ability to combine their specific structures."). The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 USPQ 545 (CCPA 1969). In this case, while Hesi et al does teach certain embodiments wherein the fragment is a F(ab')2 comprising two polymer molecules attached and Fab, Fab', or Fab'-SH wherein only one polymer molecule is attached, Hesi et al also teach additional embodiments wherein the fragment is a Fab, Fab' or Fab'-SH wherein the conjugate contains no more than about 10 polymer molecules, or no more than 5 polymer molecules, or no more than about 4 polymer molecules, or no more than about 3 polymer molecules, or no more than about 2 polymer molecules, or no more than about 1 polymer molecule (e.g., see at least pg. 23, line 15-pg. 24, line 23, pp. 28-30, pg. 30, lines 30-36). Thus, the teachings of Hesi et al are clearly not limited to the attachment of one polymer wherein attachment is at the interchain cysteine that is not substituted as suggested by applicant.

It is reiterated that Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide

labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules (, i.e., the antibody is attached to 10 or fewer PEG molecules, attached to about 5 or fewer PEG molecules, attached to about 4 or fewer PEG molecules, attached to about 3 or fewer PEG molecules (e.g., pp. 28-29)) via a cysteine residue or residues engineered into the hinge region wherein each PEG molecule may be 20,000 Da or 30,000 Da and Humphreys teach Fab' hinge region peptides (i.e., SEQ ID Nos:1-3) that efficiently generates dimer (e.g., di-Fab), and the modified hinge peptides can be reduced to expose reactive thiols to which one, two, three or more effector molecules, including PEG may be attached. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising the cysteine containing hinge peptides of SEQ ID Nos:1-3 as taught by Humphreys and reduced using the selenol-catalyzed reduction of interchain disulfides to expose reactive thiols to which PEG molecules are attached since selenol-catalyzed reduction of interchain disulfides provides a rapid method in which the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and the method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Singh et al provides evidence that reduction of interchain disulfide bonds of an antibody by selenol-catalyzed reduction provides more predictable homologous incorporation of labeled groups, is not inhibited by the presence of amines in solution and does not result in a significant decrease in affinity or stability, and selenol-catalyzed reduction of disulfide bonds in Fab fragments has been performed previously (Singh et al, pg. 148 1st col.). Applicant is reminded that obviousness does not require absolute

predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Additionally, applicants reference to the instant specification at pg. 1 that random attachment of effector molecules cannot be controlled and this can lead to loss of activity or affinity is acknowledged, however, as discussed supra, however, selenol-catalyzed reduction of disulfides as taught by Singh et al overcomes this deficiency and according to Singh results in quantitative and more predictable homologous incorporation of labeled groups and the method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 24-29, 41, 43 and 45-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of Singh et al (Analytical Biochemistry, 304(2):147-156, May 15, 2002, cited on PTO-892 mailed 2/26/2008) in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) and Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 42 filed 10/20/06).

Claims 7 and 10 of U.S. Patent No. 6,642,356 B1 are drawn to a Fab or Fab' fragment comprising one polypeptide chain that comprises the amino acid sequence of SEQ ID NO:1 (e.g., TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the Fab or Fab' fragment has one or more effector or reporter molecules attached to it. Claims 7 and 10 of U.S. Patent No. 6,642,356 B1 do not specifically teach an antibody comprising a Fab or Fab' fragment wherein the heavy chain in the fragment is not covalently bonded to the light chain and an effector molecule or polyethylene glycol (PEG) is attached to each of the interchain cysteines of CL and CH1, and wherein at least one further effector molecule is attached to a cysteine in the light chain constant region and/or to a cysteine in the heavy chain constant region, and wherein the fragment is a Fab' fragment that contains a modified hinge selected from SEQ ID Nos:1-14. These deficiencies are made for in the teachings of Singh et al and Hesi et al and Humphreys et al.

Singh et al have been described supra.

Hesi et al have been described supra.

Humphreys et al have been described supra.

The claims in the instant application are obvious variants of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced anti-IL-8 Fab, Fab', Fab-

SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al, as well as pharmaceutical compositions comprising the Fab or Fab' fragment and a pharmaceutically acceptable carrier or excipient for the treatment of inflammatory disorders.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al, as well as pharmaceutical compositions comprising the Fab or Fab' fragment and a pharmaceutically acceptable carrier or excipient for the treatment of inflammatory disorders in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Singh et al and Hesi et al and Humphreys et al because Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules via a cysteine residue or residues engineered into the hinge region wherein each PEG molecule may be 20,000 Da or 30,000 Da, as well as pharmaceutical compositions comprising the anti-IL-8 antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer and Humphreys teach engineered Fab' hinge region peptides (i.e., SEQ ID Nos:1-3) that efficiently generates dimers (e.g., di-Fab), and the modified hinge peptides can be reduced to expose reactive thiols to which one, two, three or more effector molecules, including PEG may be attached. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising the cysteine containing hinge peptides of SEQ ID Nos:1-3 as taught by Humphreys and reduced using the selenol-catalyzed reduction of interchain disulfides to expose reactive thiols to which PEG molecules are

attached since selenol-catalyzed reduction of interchain disulfides provides a rapid method in which the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and the method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al, as well as pharmaceutical compositions comprising the Fab or Fab' fragment and a pharmaceutically acceptable carrier or excipient for the treatment of inflammatory disorders in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Singh et al and Hesi et al and Humphreys et al.

Claims 24-29, 41, 43 and 45-47 are directed to an invention not patentably distinct from claims 7 and 10 of commonly assigned U.S. Patent No. 6,642,356 B1. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,642,356 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Claim Rejections - 35 USC § 112

20. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 45-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 45-46 are indefinite in the recitation "2 X 20,000 Da PEG", "3 X 20,000 Da PEG" and "2 X 30,000 Da PEG" as the exact meaning cannot be determined. It is unclear what the designations "2 X 20,000 Da PEG", "3 X 20,000 Da PEG" and "2 X 30,000 Da PEG" refer to and the phrases are not defined in the specification or the claims. Is the antibody fragment di- or tri-PEGylated, or does each of the interchain cysteines of the CL and CH1 contain two 20,000 Da PEG molecules, three 20,000 Da PEG molecules, or two 30,000 Da PEG molecules, or is some other meaning contemplated by the recitations "2 X 20,000 Da PEG", "3 X 20,000 Da PEG" and "2 X 30,000 Da PEG"?

Claim Rejections - 35 USC § 112

22. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claims 24-29, 41, 43 and 45-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 2/26/2009 has introduced NEW MATTER into the claims. As presently amended claim 24 recites that the two or three PEG effector molecules of the antibody Fab or Fab' fragment have an average molecular weight in the range from 5,000 to 30,000 Da or a derivative thereof. The response did not point out where support for presently amended claim

24 could be found in the originally filed disclosure. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP 714.02 and 2163.06 ("Applicant should therefore specifically point out the support for any amendments made to the disclosure."). Page 8 of the as filed specification discloses various ranges of the polymer, including the broader range 5,000 to 40,000 Da, however, this does not provide adequate written support for the newly presented narrower range of 5,000 to 30,000 Da. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972). The as filed specification does not disclose the presently claimed PEG range of 5,000 to 30,000 Da.

With respect to newly added claims 45-46, applicant points to Table 2 at pg. 23 of the originally filed specification. This has been fully considered but is not found persuasive. While Table 2 discloses mono-, di-, and tri-PEGylated Fab' fragments, there is insufficient written support for the interchain cysteine of the CL being attached to two or three 20,000 Da PEG molecules ("2 X 20,000 Da PEG"), or two 30,000 Da PEG molecules ("2 X 30,000 Da PEG"). Similarly, there is insufficient written support for the interchain cysteine of the CH1 being attached to two or three 20,000 Da PEG molecules ("2 X 20,000 Da PEG"), or two 30,000 Da PEG molecules ("2 X 30,000 Da PEG").

As presently amended and newly added claims 24-29, 41, 43 and 45-47 now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the presently amended and newly added claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in the present claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

24. Claims 5-7 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643